Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTAL MATERIAL

Contents

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METHODS

Trial design

The study consisted of screening, pretreatment (cell product preparation, bridging chemotherapy, and lymphodepleting chemotherapy), treatment, primary follow-up, secondary follow-up, and survival follow-up phases. Through an administrative error, the first patient was entered on the study a week before before registration on clinicaltrials.gov.

Inclusion criteria

- Aged ≥3 years at screening and ≤21 years at diagnosis
- Relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL):
    - Second or greater bone marrow (BM) relapse *or*
    - Any BM relapse after allogeneic stem cell transplant (alloSCT) and ≥6 months from SCT at the time of tisagenlecleucel infusion *or*
    - Primary refractory, defined as not achieving complete remission (CR) after 2 cycles of a standard chemotherapy regimen, or chemorefractory, defined as not achieving CR after 1 cycle of standard chemotherapy for relapsed leukemia *or*
    - Philadelphia chromosome–positive ALL intolerant of or with 2 failed lines of tyrosine kinase inhibitor (TKI) therapy or if TKI therapy is contraindicated *or*
    - Ineligible for alloSCT due to comorbid disease, contraindications to alloSCT conditioning regimen, lack of a suitable donor, prior SCT, or declined alloSCT after documented discussion about the role of SCT with a physician not part of the study team
- BM with ≥5% lymphoblasts by morphologic assessment at screening
- For relapsed patients, documentation of CD19 tumor expression in BM or peripheral blood by flow cytometry within 3 months of study entry

Maximum serum creatinine based on age and sex

	Maximum Serum Creatinine, mg/dL	
Age, years	Male Patients	Female Patients
1 to <2	0.6	0.6
2 to <6	0.8	0.8
6 to <10	1.0	1.0
10 to <13	1.2	1.2
13 to <16	1.5	1.4
≥16	1.7	1.4

- Alanine aminotransferase ≤5 times the upper limit of normal for age
- Bilirubin <2.0 mg/dL
- Minimum level of pulmonary reserve defined as grade ≤1 dyspnea and pulse oxygenation >91% on room air
- Left ventricular systolic function ≥28% confirmed by echocardiogram, or left ventricular ejection fraction ≥45% confirmed by echocardiogram or multigated acquisition images within 7 days of screening

- Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥50 at screening
- Signed written informed consent and assent forms if applicable
- Meet institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product
- Once all other eligibility criteria are confirmed, must have a leukapheresis product of nonmobilized cells received and accepted by the manufacturing site

Exclusion criteria

- Isolated extramedullary disease relapse
- Concomitant genetic syndromes associated with BM failure states, such as Fanconi anemia, Kostmann syndrome, Schwachman syndrome, or any other BM failure syndrome; patients with Down syndrome were not excluded
- Burkitt lymphoma/leukemia
- Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and no evidence of active disease
- Treatment with any prior gene therapy product
- Treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
- Active or latent hepatitis B or active hepatitis C within 8 weeks of screening, or any uncontrolled infection at screening
- Positive HIV test within 8 weeks of screening
- Grade 2 to 4 or extensive chronic graft-vs-host disease (GVHD)
- Active central nervous system (CNS) involvement by malignancy
- Received an investigational medicinal product within the 30 days prior to screening
- Pregnant or lactating
- Women of child-bearing potential and all male participants, unless using highly effective methods of contraception for 1 year after tisagenlecleucel infusion
- Therapeutic systemic doses of steroids must be stopped >72 hours prior to infusion
- Donor lymphocyte infusion must be completed >6 weeks prior to infusion
- Any systemic drug used for GVHD must be stopped >4 weeks prior to infusion
- TKIs and hydroxyurea must be stopped >72 hours prior to infusion
- The following drugs must be stopped >1 week prior to tisagenlecleucel infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25 mg/m^2, cytosine arabinoside <100 mg/m^2/day, asparaginase (nonpegylated)
- The following drugs must be stopped >2 weeks prior to tisagenlecleucel infusion: salvage chemotherapy (e.g., clofarabine, cytosine arabinoside >100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
- Pegylated asparaginase must be stopped >4 weeks prior to tisagenlecleucel infusion
- CNS disease prophylaxis must be stopped >1 week prior to tisagenlecleucel infusion
- Radiation therapy at non-CNS site must be completed >2 weeks prior to tisagenlecleucel infusion
- CNS-directed radiation must be completed >8 weeks prior to tisagenlecleucel infusion

- Anti–T-cell antibodies within 8 weeks of infusion

Manufacture

Autologous leukapheresis products were collected and cryopreserved at the individual clinical sites and shipped to the manufacturing facilities (Morris Plains, NJ, USA [n = 63], and Leipzig, Germany [n = 12]); CD3/CD28 antibody–coated beads were used to enrich for and activate T cells, which were then transduced with the tisagenlecleucel chimeric antigen receptor (CAR) via a lentiviral vector and expanded ex vivo for approximately 10 days; the tisagenlecleucel cells were concentrated and cryopreserved for shipment back to the clinical site. Samples were removed for release testing as specified in a US Food and Drug Administration–accepted Investigational New Drug Application. From May 2015 to February 2017, patients received a single infusion of 0.2 to 5×10^6/kg (patients ≤50 kg) or 0.1 to 2.5×10^8 (patients >50 kg) autologous tisagenlecleucel transduced cells. Patients were infused with the maximum cell dose within this range that could be individually manufactured.

Efficacy analysis

CR classification required all of the following criteria be met: <5% lymphoblasts in BM by morphology, circulating blasts <1% in peripheral blood, no evidence of extramedullary disease, neutrophils $>1.0\times10^9$/L, platelets $>100\times10^9$/L, and no platelet and/or neutrophil transfusions within 7 days of peripheral blood sample for disease assessment. CR with incomplete blood count recovery (CRi) was defined by all criteria for CR, except that patients had ≥1 of the following: neutrophils $\leq1.0\times10^9$/L, platelets $\leq100\times10^9$/L, or platelet/neutrophil transfusions within 7 days of peripheral blood sample for disease assessment.

Analysis sets

- Screened set: all patients who signed informed consent and were screened for the study (n = 107)
- Enrolled set: all patients who completed screening phase and were eligible and enrolled, and whose leukapheresis product was received and accepted by the manufacturing facilities (n = 92)
- Full analysis set: all patients who received an infusion of tisagenlecleucel (n = 75)
- Safety set: all patients who received an infusion of tisagenlecleucel (identical to the full analysis set, n = 75)
- Cellular kinetics set: same as the full analysis set
- Per-protocol set: a subset of the full analysis set who met the major requirements of the protocol (n = 68)
- Interim analysis efficacy set: first 50 patients who received tisagenlecleucel infusion (n = 50)

Safety

Adverse events (AEs) were assessed in the safety population per the Common Terminology Criteria for Adverse Events version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), with the exception of cytokine release syndrome (CRS), which was graded according to the Penn/CHOP scale[1,2] and managed per a protocol-specific algorithm (Supplementary Table S8) and GVHD, which was graded using protocol-defined criteria.[3,4] AEs of special interest were defined based on experience from ongoing tisagenlecleucel clinical studies and considered to be

attributed to tisagenlecleucel.[5,6]

Cellular kinetics

Cellular kinetics of tisagenlecleucel postinfusion were determined from peripheral blood using qualitative polymerase chain reaction methods. Cellular kinetic parameters were derived using traditional pharmacokinetic principles and reported by response category and by dose. A validated assay (Genoptix) was used to detect the CD19 CAR transgene sequence.[7]

Statistical analysis

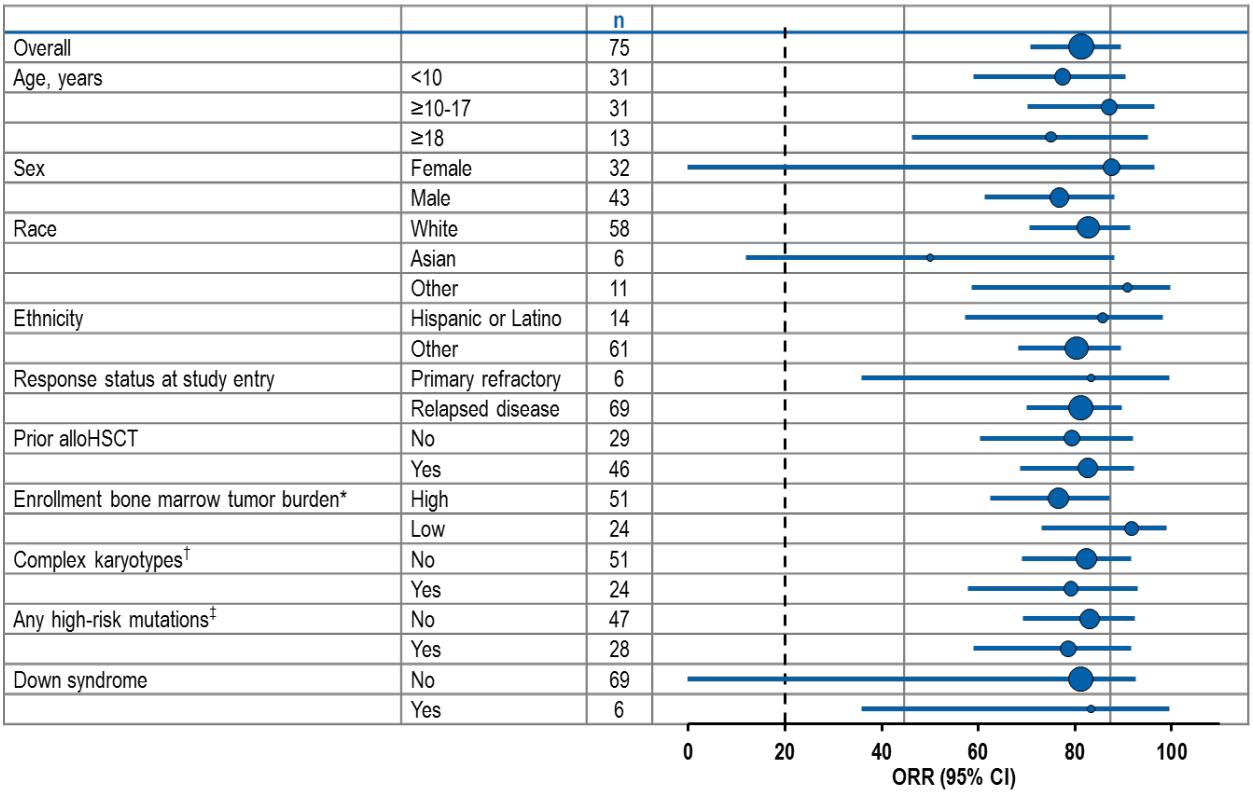
The primary endpoint was independent review committee–assessed overall remission rate (ORR; CR/CRi) by month 3 in patients in the full analysis set. Best overall response of CR or CRi required no clinical evidence of relapse ≥4 weeks after initial achievement of CR or CRi. Study accrual of 76 patients infused provides >95% power to reject null hypothesis of 20% under alternative hypothesis of ≥45% at overall 1-sided 2.5% level of significance. Key secondary endpoints included (1) ORR within 3 months with tisagenlecleucel from the US manufacturing facility, (2) CR/CRi with undetectable minimal residual disease (MRD; <0.01%) by multiparameter flow cytometry from both manufacturing facilities (United States and Germany), and (3) CR/CRi with undetectable MRD with tisagenlecleucel from the US manufacturing facility. For the key secondary endpoint of MRD-negative remission rate, the null hypothesis of MRD-negative remission rate of 20% against alternative hypothesis of 34% was tested sequentially only after the primary endpoint of ORR was met.

The interim analysis was planned after the first 50 infused patients completed 3 months of follow-up or discontinued. The primary endpoint was considered met at the interim analysis if the 1-sided *P* value was <0.0057. Key secondary endpoints were tested sequentially (after the primary endpoint was significant) to control overall alpha.

The results presented are from the updated analysis when 75 patients (the full analysis set and basis of the ORR, DOR, and cellular kinetic analyses) who received tisagenlecleucel had completed 3 months of follow-up or discontinued earlier. For time-to-event analyses, Kaplan-Meier curves were used to estimate survival distributions after infusion. All statistical tests were performed using SAS software (version 9.4). We have presented the 95% CIs.

Figure S1. ORR Within 3 Months by Independent Review Committee Assessment—Forest Plot for Subgroups (full analysis set).

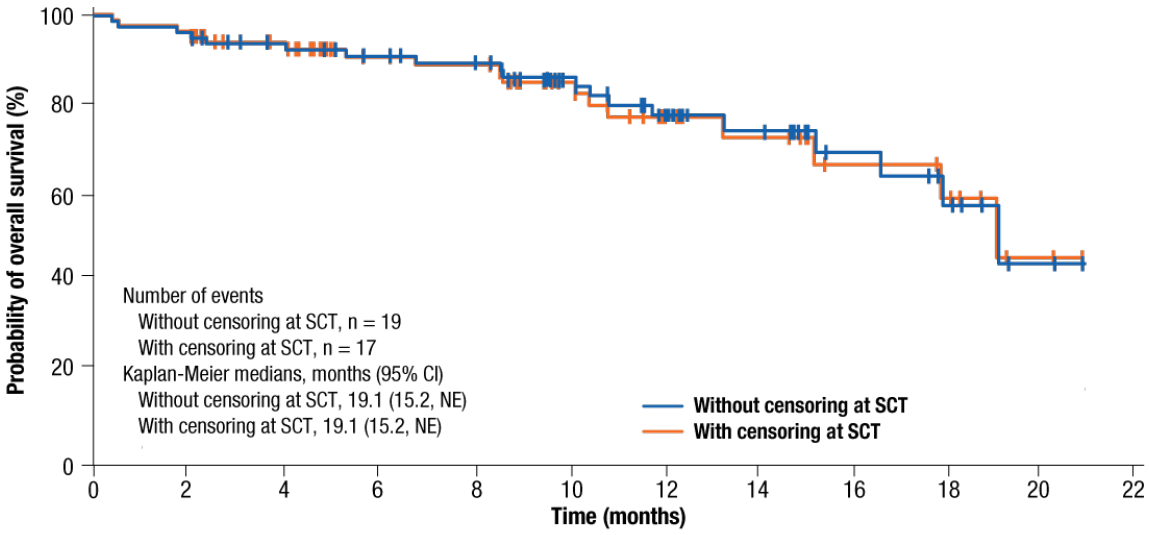
The size of each dot is proportional to the number of patients in that grouping. The 95% CIs are exact Clopper-Pearson CIs calculated for each subgroup.



* Low disease burden, <50% lymphoblasts in bone marrow; high disease burden, ≥50% lymphoblasts in bone marrow. † ≥5 unrelated abnormalities. ‡ *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*–like gene signature, or complex karyotype.

ORR within 3 months for patients who received infusion of tisagenlecleucel at or before the median time of 45 days was 80% (95% CI, 64%-91%) compared with 83% (95% CI, 67%-94%) for patients who were infused at greater than the median time from enrollment to infusion.

Figure S2. Overall Survival With and Without Censoring at the Time of Allogeneic Stem Cell Transplant. Overall survival in the 75 infused patients from the date of tisagenlecleucel infusion to the date of death due to any reason. Tick marks indicate the time of censoring.

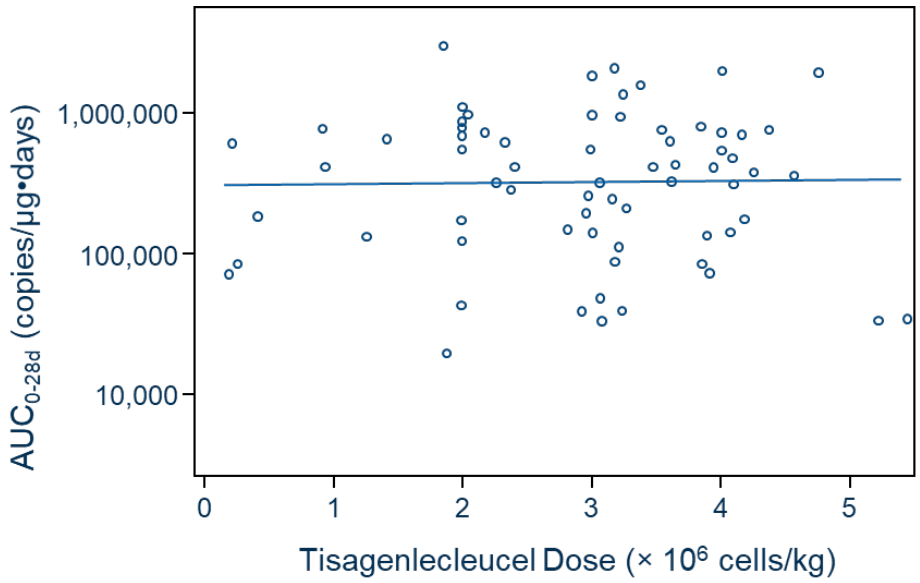


Patients at risk												
Without censoring at SCT	75	72	64	58	55	40	30	20	12	8	2	0
With censoring at SCT	75	72	60	48	45	31	21	15	9	7	2	0

Figure S3. Cellular Kinetics of Tisagenlecleucel After Infusion.

(A) C_{max} and (B) $AUC_{0\text{-}28}$ of tisagenlecleucel by weight-adjusted tisagenlecleucel transduced viable cell dose together with the regression line. The cellular kinetics of tisagenlecleucel after infusion were determined from peripheral blood using qualitative polymerase chain reaction methods to detect the CD19 CAR transgene sequence. $AUC_{0\text{-}28d}$, area under the curve from time zero to day 28; C_{max}, maximum serum concentration; Conc, concentration.

A.



B.

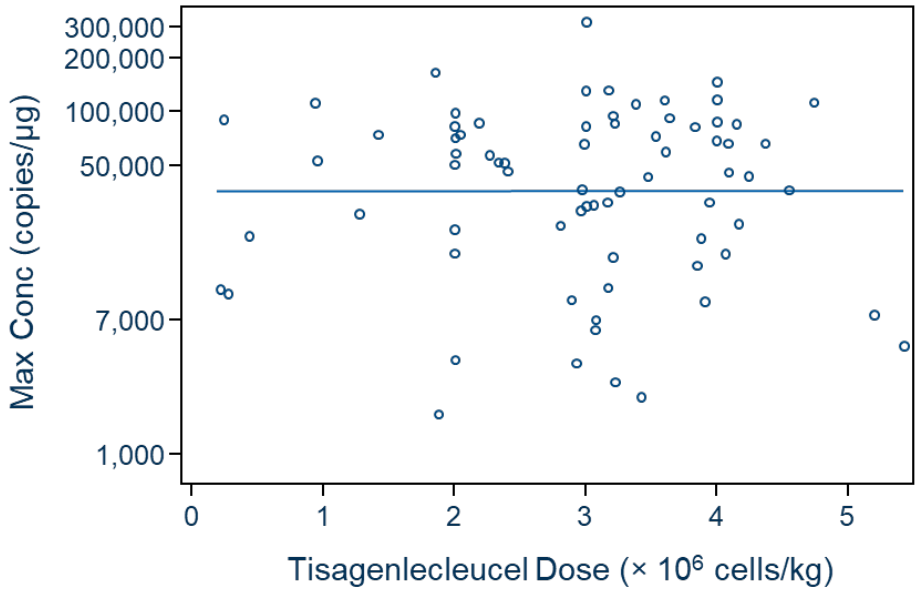


Figure S4. Kaplan-Meier Analysis of B-Cell Aplasia.
Time to B-cell recovery, defined as the time from onset of remission (regardless of confirmation in all infused patients) to reaching ≥1% CD19+ cells in viable white blood cells or ≥3% CD19+ cells in lymphocytes in blood. There were 13 events; median time to B-cell recovery was not reached.

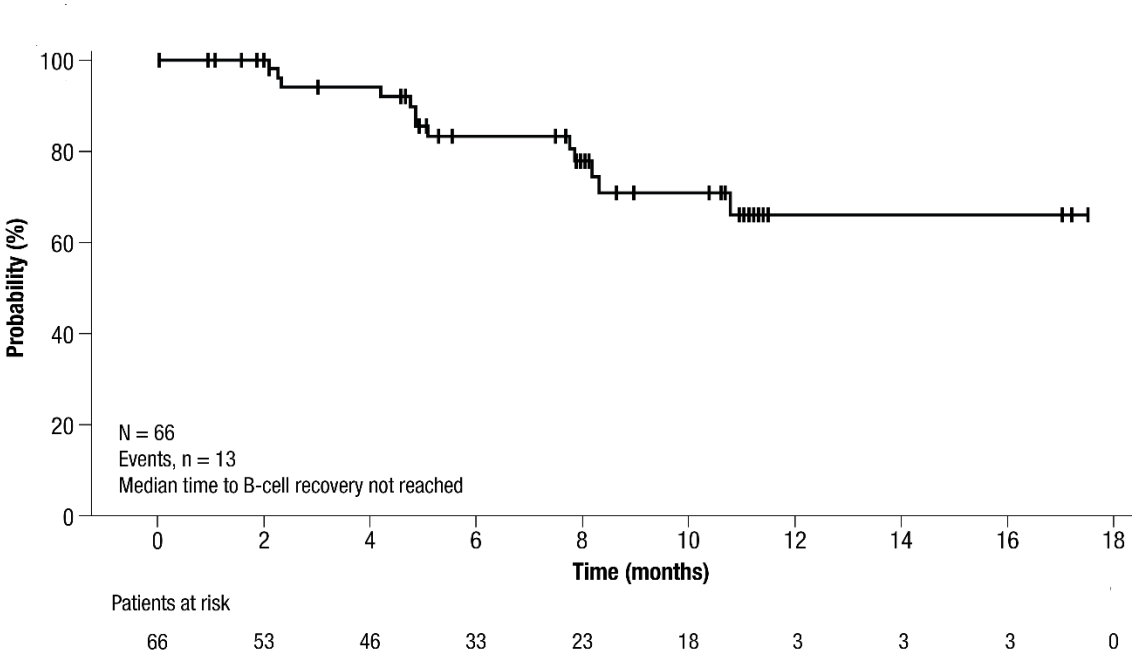


Figure S5. Serum Biomarkers Over Time by Grade of Cytokine Release Syndrome (CRS).
(A) IL-6, (B) interferon gamma, (C) ferritin, and (D) C-reactive protein levels in patients with no CRS, grade 1/2 CRS, grade 3 CRS, and grade 4 CRS.

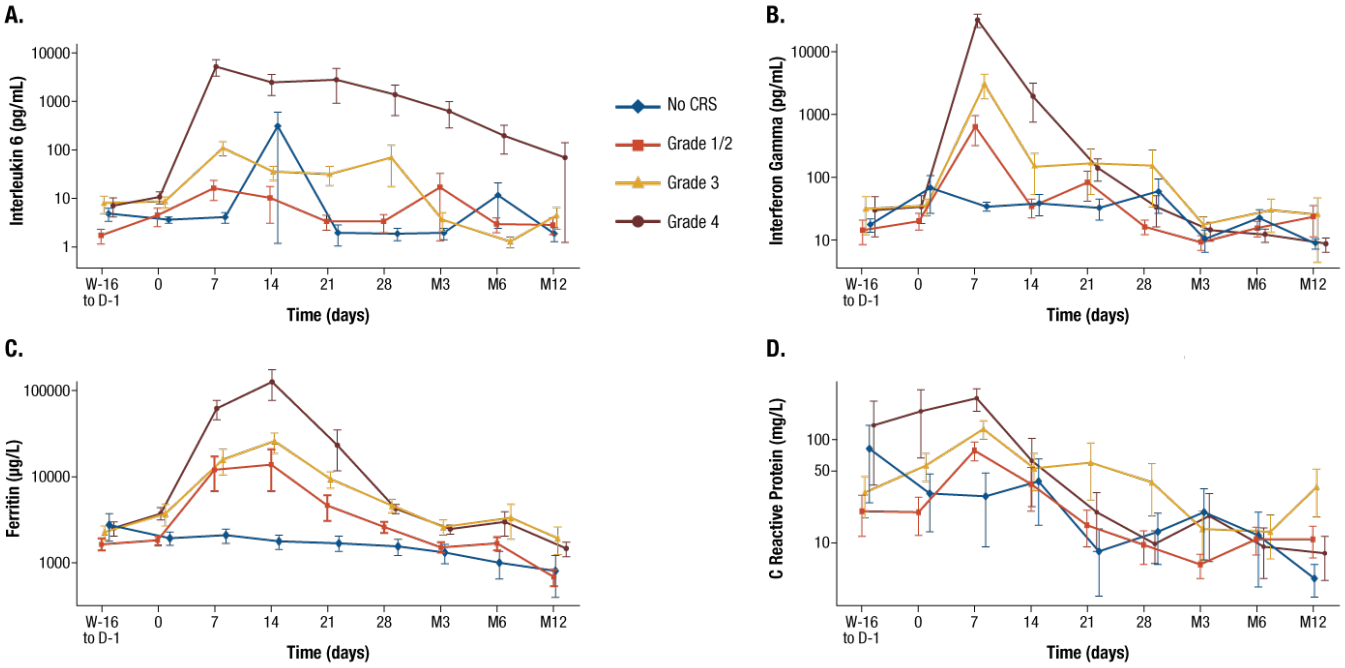


Table S1. Patient Demographics and Baseline Clinical Characteristics.

	Patients (N = 75)
Age, median (range), years	11 (3-23)
Male, n (%)	43 (57)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)
CNS status classification, n (%)*	
CNS-1	63 (84)
CNS-2	10 (13)
CNS-3	1 (1)
Unknown	1 (1)
High-risk genomic lesions, n (%)[†]	28 (37)
Down syndrome, n (%)	6 (8)

CNS, central nervous system.

* The most current assessment on or prior to the date of enrollment. [†] *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*-like gene signature, or complex karyotype (≥5 unrelated abnormalities).

Table S2. Tisagenlecleucel Dose Administration.*

	Patients (N = 75)
Median time from enrollment to infusion (range), days	45 (30-105)
Tisagenlecleucel transduced cell dose infused (10^8 cells)	
Mean (SD)	1.1 (0.60)
Median	1.0
Min-max	0.03-2.6
Weight-adjusted tisagenlecleucel dose (10^6 cells/kg)	
Mean (SD)	2.9 (1.2)
Median	3.1
Min-max	0.2-5.4
Total cell dose infused (10^8 cells)	
Mean (SD)	5.5 (4.0)
Median	4.7
Min-max	0.2-20

ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; max, maximum; min, minimum.
* The planned dose range was selected based on available data from patients with CLL, adult ALL, and pediatric ALL treated with tisagenlecleucel.[1,8,9,10]

Table S3. Response Rates.

Response Rates	Patients (N = 75)
Primary endpoint	
ORR (CR + CRi) within 3 months, n (%)*	61 (81)
95% CI, %	71 to 89
BOR, n (%)	
CR	45 (60)
CRi	16 (21)
No response	6 (8)
Unknown†	8 (11)
Secondary endpoints	
Achieved BOR of CR or CRi within 3 months with MRD-negative BM, n (%)‡	61 (81)
95% CI, %	71 to 89
Day 28 response, n (%)	
CR	23 (31)
CRi	37 (49)
No response	6 (8)
Unknown	9 (12)
Sensitivity analysis (intent to treat)	N = 92
ORR (CR + CRi) of enrolled set, n (%)	61 (66)
95% CI, %	56-76

alloSCT, allogeneic stem cell transplant; BM, bone marrow; BOR, best overall response; CR, complete remission; CRi, CR with incomplete blood count recovery; MRD, minimal residual disease; ORR, overall remission rate.

* In patients infused with tisagenlecleucel ≥3 months prior to data cutoff. † The response of 8 patients (11%) was unknown (2 patients died before assessment [acute lymphoblastic leukemia and cerebral hemorrhage]; 1 patient with remission at the day 28 assessment died prior to the 3-month assessment [encephalitis]; 1 patient died with indeterminate bone marrow remission [systemic mycosis]; 1 patient

with unconfirmed remission proceeded to alloSCT; 2 patients achieved bone marrow remission but did not have a cerebral spinal fluid assessment by lumbar puncture postinfusion, and 1 patient showed an absence of marrow blasts by pathology but marrow and blood differentials were not available). ‡ MRD-negative = MRD <0.01%.

Table S4. Tisagenlecleucel Cellular Kinetics.
Statistical analysis was not feasible due to the low number of patients with no response (NR; n = 6).

Parameter	**Statistics**	**CR/CRi (n = 60)***	**NR (n = 6)***
$AUC_{0\text{-}28d}$, copies/µg DNA × days	n	59	5
	Geometric mean (CV%)	315,000 (186)	301,000 (117)
	Fold-change between CR/CRi and NR	1.04	—
C_{max}, copies/µg DNA	n	60	6
	Geometric mean (CV%)	36,100 (154)	20,900 (187)
	Fold-change between CR/CRi and NR	1.72	—
C_{last}, copies/µg DNA	n	60	6
	Geometric mean (CV%)	281 (249)	1450 (341)
T_{max}, days	n	60	6
	Median	10	20
	[Min-max]	[6-28]	[13-63]
$T_{1/2}$, days	n	47	2
	Geometric mean (CV%)	23 (199)	3.6 (238)
T_{last}, days	n	60	6
	Median	168	49
	[Min-max]	[20-617]	[14-376]

AUC, area under the curve; $AUC_{0\text{-}28d}$, AUC from time zero to day 28; C_{last}, last quantifiable level of tisagenlecleucel transgene; C_{max}, maximum concentration; max, maximum; min, minimum; NR, no response; $T_{1/2}$, half-life; T_{last}, time of last quantifiable level of tisagenlecleucel transgene; T_{max}, time to reach peak concentration.
* Number of patients with data available for each cellular kinetic parameter varied.

Table S5. Nonhematologic AEs Occurring at Any Time After Tisagenlecleucel Infusion, Regardless of Study Drug Relationship.

	Patients (N = 75)		
Adverse Event, n (%)	**All Grades**	**Grade 3**	**Grade 4**
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Pyrexia	30 (40)	8 (11)	2 (3)
Decreased appetite	29 (39)	10 (13)	1 (1)
Hypotension	22 (29)	8 (11)	7 (9)
Aspartate aminotransferase increased	20 (27)	8 (11)	3 (4)
Hypokalemia	20 (27)	9 (12)	2 (3)
Hypoxia	18 (24)	10 (13)	4 (5)
Hypophosphatemia	18 (24)	8 (11)	1 (1)
Blood bilirubin increased	13 (17)	9 (12)	0

Cutoff; grade 3 or 4 rates of ≥10%.

Table S6. Grade 3 or 4 Adverse Events Suspected to Be Tisagenlecleucel-Related Occurring in ≥2 Patients.

n (%)	≤8 Weeks After Tisagenlecleucel Infusion (N=75)		>8 Weeks to 1 Year After Tisagenlecleucel Infusion (n=70)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Patients with ≥1 grade 3 or 4 adverse event	**19 (25)**	**33 (44)**	**8 (11)**	**4 (6)**
Cytokine release syndrome	16 (21)	19 (25)	—	—
Hypotension	7 (9)	6 (8)	—	—
Lymphocyte count decreased	5 (7)	4 (5)	1 (1)	—
Hypoxia	5 (7)	3 (4)	—	—
Blood bilirubin increased	8 (11)	—	—	—
Neutrophil count decreased	1 (1)	6 (8)	1 (1)	1 (1)
Aspartate aminotransferase increased	5 (7)	2 (3)	—	—
Pyrexia	5 (7)	2 (3)	—	—
White blood cell count decreased	—	7 (9)	—	—
Platelet count decreased	3 (4)	4 (5)	—	—
Decreased appetite	6 (8)	1 (1)	—	—
Acute kidney injury	3 (4)	3 (4)	—	—
Hypophosphatemia	5 (7)	1 (1)	—	—
Hypokalemia	6 (8)	—	—	—
Pulmonary edema	4 (5)	1 (1)	—	—

Thrombocytopenia	—	4 (5)	—	1 (1)
Encephalopathy	4 (5)	—	—	—
Alanine aminotransferase increased	4 (5)	—	—	—
Fluid overload	4 (5)	—	—	—
Immunodeficiency	3 (4)	—	1 (1)	—
Neutropenia	—	3 (4)	—	—
Respiratory failure	—	3 (4)	—	—
Blood creatinine increased	2 (3)	1 (1)	—	—
Pleural effusion	2 (3)	1 (1)	—	—
Tachycardia	2 (3)	1 (1)	—	—
Hemophagocytic lymphohistiocytosis	2 (3)	1 (1)	—	—
Anemia	3 (4)	—	—	—
Delirium	3 (4)	—	—	—
Hypocalcemia	3 (4)	—	—	—
Left ventricular dysfunction	3 (4)	—	—	—
Tachypnea	3 (4)	—	—	—
Tumor lysis syndrome	3 (4)	—	—	—
Acute respiratory distress syndrome	—	2 (3)	—	—
Multiple organ dysfunction syndrome	—	2 (3)	—	—
Blood creatine phosphokinase increased	1 (1)	1 (1)	—	—
Hypertriglyceridemia	1 (1)	1 (1)	—	—

Urine output decreased	1 (1)	1 (1)	—	—
Abdominal pain	2 (3)	—	—	—
Dyspnea	2 (3)	—	—	—
Headache	2 (3)	—	—	—
Hypogammaglobulinemia	2 (3)	—	—	—
Hyperglycemia	2 (3)	—	—	—

Table S7. Serious AEs Occurring in ≥ 2 Patients at Any Time After Tisagenlecleucel Infusion, Regardless of Study Drug Relationship

	Patients (N = 75)		
Adverse Event, n (%)*	**All Grades**	**Grade 3**	**Grade 4**
Cytokine release syndrome	47 (62.7)	15 (20.0)	19 (25.3)
Febrile neutropenia	15 (20.0)	14 (18.7)	1 (1.3)
Hypotension	8 (10.7)	1 (1.3)	7 (9.3)
Pyrexia	7 (9.3)	1 (1.3)	0
Acute kidney injury	5 (6.7)	2 (2.7)	3 (4.0)
Hypoxia	5 (6.7)	3 (4.0)	2 (2.7)
Respiratory failure	5 (6.7)	0	5 (6.7)
Back pain	3 (4.0)	2 (2.7)	0
Cardiac arrest	3 (4.0)	0	3 (4.0)
Acute respiratory distress syndrome	2 (2.7)	0	2 (2.7)
Aspartate aminotransferase increased	2 (2.7)	2 (2.7)	0
Cardiac failure	2 (2.7)	1 (1.3)	1 (1.3)
Disseminated intravascular coagulation	2 (2.7)	1 (1.3)	0
Encephalitis	2 (2.7)	0	2 (2.7)
Mental status changes	2 (2.7)	1 (1.3)	0
Multiple organ dysfunction syndrome	2 (2.7)	0	2 (2.7)
Pancreatitis	2 (2.7)	2 (2.7)	0
Pleural effusion	2 (2.7)	1 (1.3)	1 (1.3)
Respiratory distress	2 (2.7)	0	1 (1.3)
Respiratory syncytial virus infection	2 (2.7)	2 (2.7)	0
Rhinovirus infection	2 (2.7)	1 (1.3)	0
Septic shock	2 (2.7)	0	2 (2.7)
Staphylococcal bacteremia	2 (2.7)	2 (2.7)	0
Tumor lysis syndrome	2 (2.7)	1 (1.3)	1 (1.3)

Upper respiratory tract infection	2 (2.7)	2 (2.7)	0

* Events may have occurred after the start of new anticancer therapy.

Table S8. Neurological Adverse Events According to Cytokine Release Syndrome Grade.

Cytokine Release Syndrome	N	Any-Grade Neurological Events, n (%)	Grade 3 Neurological Events, n (%)
None	17	4 (24)	1 (6)
Grade 1/2	23	7 (30)	1 (4)
Grade 3	16	7 (44)	2 (13)
Grade 4	19	12 (63)	6 (32)

Table S9. CRS Management Algorithm.

Pretreatment
• Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine • Prophylaxis for complications of TLS as appropriate
Tisagenlecleucel Infusion **Prodromal Syndrome:** low-grade fevers, fatigue, anorexia (hours to days)
• Observation, rule out infection (surveillance cultures) • Antibiotics per local guidelines (febrile neutropenia) • Symptomatic support
Symptom Progression: High fevers, hypoxia, mild hypotension First-Line Management: • Oxygen, fluids, low-dose vasopressor support, antipyretics • Monitor/manage complications of TLS
Further Symptom Progression: • Hemodynamic instability despite intravenous fluids and moderate to "high-dose" vasopressor[1] support *or* • Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirements including high-flow oxygen and/or need for mechanical ventilation *or* • Rapid clinical deterioration Second-Line Management: Tocilizumab: IV Infusion Over 1 Hour • Patient weight <30 kg: 12 mg/kg i.v. • Patient weight ≥30 kg: 8 mg/kg i.v. (maximum dose, 800 mg) Hemodynamic and respiratory support
Lack of Clinical Improvement While Awaiting Tocilizumab Response Third-Line Management: • Consider other diagnosis causing clinical deterioration (i.e., sepsis, adrenal insufficiency) • If no improvement with first dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper **after** hemodynamic normalization): o 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. Because steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement • If no response to steroids within 24 hours, consider second dose of tocilizumab (dosed as above) • Hemodynamic and respiratory support
Lack of Clinical Improvement While Awaiting Response to Third-Line Management Fourth-Line Management: • Consider other diagnosis causing clinical deterioration (i.e., sepsis, adrenal insufficiency) • If no response to steroids and second dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour • Hemodynamic and respiratory support

Lack of Clinical Improvement While Awaiting Response to Fourth-Line Management
Fifth-Line Management:

- Consider other diagnosis causing clinical deterioration (i.e., sepsis, adrenal insufficiency)
- In ongoing CRS despite prior therapy, consider anti–T-cell therapies such as cyclophosphamide, antithymocyte globulin, or alemtuzumab
- Hemodynamic and respiratory support

CRS, cytokine release syndrome; i.v., intravenous; TLS, tumor lysis syndrome.

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